PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lupski *et al.*	Group Art Unit: 1637
Application Serial No.: 10/021,955	Examiner: Chunduru, S.
Filed: December 13, 2001	Atty. Dkt. No.: P02086US1
For: Baylor College of Medicine	Title: Defects in Periaxin Associated with Myelinopathies

REPLY BRIEF

Commissioner for Patents
Washington, D.C. 20231

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APPENDICES

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Date: October 24, 2005

Monica T. Owens

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REPLY BRIEF

MS Appeal Brief
Commissioner of Patents
Washington, D.C. 20231

Sir:

Appellant hereby submits an original and two copies of this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer mailed August 23, 2005 (the "Answer"). Appellants file herewith a Request for Oral Hearing and the requisite fee.

The fee for filing this Reply Brief is $500.00 and is enclosed herewith. Please date stamp and return the attached postcard as evidence of receipt.

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I. REAL PARTY IN INTEREST

The real parties in interest are still the assignee, Baylor College of Medicine, and the licensee, Athena Diagnostics, Inc.

II. RELATED APPEALS AND INTERFERENCES

There are still no related appeals or interferences.

III. STATUS OF THE CLAIMS

The status of the claims is noted in the Appeal Brief. A copy of the pending claims is attached as Appendix 1.

IV. STATUS OF AMENDMENTS

There are still no outstanding amendments in the pending claims.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The summary of the claimed subject matter is noted in the Appeal Brief.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-7, 35-40, and 42-61 remain rejected under 35 U.S.C. §112, first paragraph as allegedly failing to meet the enablement requirement.

VII. GROUPING OF CLAIMS

The Examiner states in the Answer that the rejection of claims 1-7, 35-40, 42-61 stand or fall together because Appellants' brief did not include a statement that this grouping of the claims does not stand or fall together and reasons in support thereof.

Appellants respectfully note that a statement and reasons were presented in section VII. C. of Appellants' brief, and as noted in the Federal Register (Vol. 69, No. 155, p. 49962), it is not required by Appellants to state this in a separate section. Appellants provide this section herein solely to bring the attention of this issue to the Board and to request rectification.

Therefore, Appellants request acknowledgement by the Office that the claims are grouped as noted in Appellants' brief. Nevertheless, Appellants reiterate the grouping of the claims set forth in Appellants' brief.

The claims do not stand or fall together but are grouped as being separately patentable. In particular, Appellants considers separate patentability for the grouping of the claims as follows: claims 1-7; claims 35-40 and 42; claims 43-48, claims 49-56; claims 57-60; and claim 67. All of the noted groups are separately patentable from each of the other groups because each grouping of claims concerns a different scope of the invention from the other groups, and the rejection of whether or not Appellants have provided sufficient disclosure to enable the claims is directly related to their scope. Appellants reiterate that each group of the claims is enabled.

VIII. ARGUMENT

Appellants address herein the Examiner's comments on the Brief.

Contrary to the Examiner's arguments, the specification enables the breadth of the pending claims. The Examiner is erroneously holding the claims to an improper standard by alleging that the specification lacks predictable correlation for a PRX alteration corresponding to any myelinopathy. Appellants position is consistent with the decision of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970), which states that the scope of the enablement must only bear a "reasonable correlation" to the scope of the claims. Therefore, a predictable correlation is not the standard by which Appellants' claims should be judged.

Appellants assert that they have met the reasonable correlation standard set by the courts by showing a periaxin mutation for the exemplary myelinopathy DSN and by describing the highly-related myelinopathies, particularly given their art-recognized phenotypic similarities (such as those described in paragraphs **[0074]** to **[0083]**). This is further confirmed by others that have subsequently identified periaxin mutations in myelinopathies within the spectrum of myelinopathies that include DSN, commensurate with Appellants' teaching.

Appellants' claims and specification are also consistent with the decision of *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)), which states that it is not a requirement to test all embodiments of the invention. Therefore, it is not required to list each and every periaxin mutation that results in myelinopathy, given that a representative

number of mutations have been provided, and one of skill in the art is taught in the specification methods of how to obtain others, at least in paragraphs **[0235]** to **[0250]**. For example, at paragraphs **[0244]** to **[0246]**, **[0249]-[0250]**, and **[0264]-[0282]**, Appellants provide exemplary methods for identifying mutations in a sequence and associating those mutations with an exemplary myelinopathy, DSN. Therefore, Appellants have met the standard determined by the courts of providing a reasonable correlation to satisfy enablement.

Appellants position is also consistent with court cases that determined that where experiments may be necessary to practice the invention, a considerable amount of routine experimentation is permissible, especially where the Appellants' specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976). As noted above and contrary to the Examiner's assessment, Appellants ***do*** provide a reasonable amount of guidance.

Furthermore, the courts have determined that time-consuming experiments are acceptable if the type of experimentation is standard in the art, and the genetic studies for determining whether or not a PRX alteration is diagnostic is most definitely standard in the art, as noted in the specification at least at paragraphs **[0244]** to **[0246]**, **[0249]-[0250]**, and **[0264]-[0282]** and in the declaration provided by the expert. An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance (*In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)), and ***the experimentation may even be complex*** (*In re Wands*, 858 F.2d 737, 8 USPQ2d 1404 (Fed. Cir. 1985); *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)) ***and considerable in quantity*** (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))) ***if it is routine***. Appellants also respectfully remind the Board that disclosure of well-known techniques or scientific principles to those of skill in the art is not required. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert.*

denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBC v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

Appellants assert that the Examiner is in error for alleging that the Appellants have provided an insufficient amount of guidance to enable claims for any alteration of PRX associated with any myelinopathy. In particular, the courts have determined that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970), and the courts have also determined that guidance is not necessary to those skilled in the art, particularly when it is well-recognized that the skill in the art of molecular biology is quite high (*Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986).

During prosecution, Appellants provided multiple papers published postfiling of the application that described periaxin alterations that are associated with myelinopathies other than DSN. Given that Appellants taught in the original disclosure that alterations in periaxin are indicative of myelinopathies and provided standard but exemplary methods for identifying them, these subsequent papers are ***strong evidence*** that Appellants in fact did provide how to make and use the invention, and the claims are thus enabled. The Examiner dismisses these articles by alleging that they still do not provide a predictable correlation for a PRX mutation and myelinopathy, but as Appellants have discussed above, this is not a proper standard.

The Examiner erroneously states that the claims are not enabled because there are several examples in the references and in the specification that describe unaffected individuals that have an altered allele. Appellants respectfully state that the Examiner must misunderstand the art of genetics. Appellants claims encompass testing an individual for whether or not they are a homozygote and therefore have two alterations (defective alleles), but also encompass testing an individual for whether or not they are a heterozygote and therefore have one alteration (defective allele). Although the heterozygote has only one alteration, it is still informative for that individual to be aware of being a carrier for the disease. A skilled artisan is also aware that there are polymorphisms in PRX sequences that are not associated with disease even when present on both alleles, yet the skilled artisan is aware how to differentiate among the possibilities, as noted in the declaration by the expert Dr. Lupski. Determination of whether or not an alteration is a recessive mutation and present on one allele, a recessive mutation and present on two alleles, or a

polymorphism, for example, is regularly performed in the art. The references published postfiling of the application reporting additional periaxin mutations in other myelinopathies is proof of this point.

In addition to being an improper standard, whether or not one can ***predict*** if a particular alteration is disease-causing is irrelevant, because the studies required to demonstrate the nature of the alteration are routine and not undue. Given the expert's statements regarding what was known in the art and the successful practice of others employing Appellants' methods to identify myelinopathy disease-causing periaxin alterations, it is clear that even if it was trial and error, this was not undue and that a ***reasonable*** amount of routine experimentation ***was*** employed.

At the very least, claims 4 and 40 are certainly enabled, given that Appellants list very specific myelinopathies therein. Furthermore, at the very least claim 58 regards a prominent sensory neuropathy, which does not include a wide range of myelinopathies. These pending claims do not cover myelinopathies resulting from mutations in other polynucleotides, and the scope is not so broad as the Examiner contends. Appellants also assert that at the very least, claims 57 and 61 are enabled, as they encompass methods of identifying individuals ***suspected*** of having a myelinopathy or being a carrier thereof.

Also, Appellants stress that independent claims 35 and 49 are directed to respectively detecting the presence or absence of a mutation or detecting a polymorphism in PRX, both claims in the context of being associated with a myelinopathy. Consistent with the grouping of the claims by Appellants, the scope of these claims is different from independent claims 1 and 43, directed to diagnosing myelinopathy. Appellants have most certainly provided enough guidance to at least associate a periaxin mutation or polymorphism with a myelinopathy. Moreover, claim 35 recites that the myelinopathy results from a periaxin mutation, so therefore one of skill in the art can test for the presence/absence of such mutations. The mutations are directly associated with myelinopathy and would help to identify whether an individual is affected or is a carrier.

Appellants also reiterate that at least claims 4, 40, and 51 directed to very specific myelinopathies are enabled, given that it is not undue to test for the alteration in individuals that have these particular myelinopathies or of being suspected of having one of these specific myelinopathies. The amount and type of studies for testing alterations for these specific myelinopathies are reasonable in scope, and it would not be an undue burden or require inventive

input for a skilled artisan to practice the invention of these claims. Likewise, at least claims 7, 36, 37, 42, and 48 are clearly enabled, given that it is not undue to test for these very particular alterations in individuals having a myelinopathy or suspected of having a myelinopathy.

The crux of the Examiner's argument is that there is no predictable correlation for any alteration in PRX to be diagnostic for any myelinopathy. However, Appellants assert that this is an improper standard and a representative number of exemplary periaxin mutations and a listing of exemplary myelinopathies were provided in the specification, in addition to methods to determine other diagnostic alterations. Considering that additional researchers practiced the invention shortly after the filing of Appellants' application, there was no undue experimentation to practice the invention.

Appellants respectfully request reversal of the Examiner's rejection.

IX. CONCLUSION

Appellants have provided arguments that overcome the pending rejection. Appellants respectfully submit that the Answer's conclusions that the rejection of the claims should be sustained are unwarranted. It is therefore requested that the Board overturn the rejection of the Action.

Please date stamp and return the enclosed postcard to evidence receipt of this document.

Dated: Oct. 24, 2005

Respectfully submitted,

By _____

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APPENDIX 1

PENDING CLAIMS

1. A method of diagnosing myelinopathy in an individual, said myelinopathy resulting from a periaxin alteration in the individual, comprising the steps of:

obtaining a sample containing nucleic acid from said individual;

assaying said sample for an alteration in a periaxin polynucleotide, wherein said assaying step provides said diagnosis.

2. The method of claim 1, wherein said periaxin polynucleotide is SEQ ID NO:76.

3. The method of claim 1, wherein said periaxin polynucleotide is SEQ ID NO:1, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, or SEQ ID NO:77.

4. The method of claim 1, wherein said myelinopathy is selected from the group consisting of Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSN), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS).

5. The method of claim 1, wherein said assaying step further comprises a polymerase chain reaction.

6. The method of claim 5, wherein primers for said polymerase chain reaction are selected from the group consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID

NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, and SEQ ID NO:26.

7. The method of claim 1, wherein said alteration is 3775G>A, 1216G>A, 4075-4077d, 1483G>C, 3394A>G, 3248C>G, 2763A>G, 2645C>T, 306C>T, 1491C>G, 2655T>C, 2145T>A, 1102C>T, 2289delT, 2787delC, 2857C>T, or 247ΔC.

35. A method of detecting the presence or absence of a mutation associated with a myelinopathy, said myelinopathy resulting from a periaxin mutation in the individual, the method comprising:

a) isolating a test nucleic acid from a subject, said test nucleic acid comprising a periaxin polynucleotide;

b) comparing the test nucleic acid to a reference wild-type periaxin polynucleotide; and

c) determining the differences between the test nucleic acid and the reference wild-type periaxin polynucleotide, wherein the differences are mutations in the periaxin polynucleotide of the subject, and wherein said detection of the presence or absence of the mutation is therein provided.

36. The method of claim 35, wherein said mutation is 2145T>A, 1102C>T, 2289delT, 2787delC, 2857C>T, or 247ΔC.

37. The method of claim 35, wherein said mutation encodes a defect of a periaxin polypeptide, wherein the defect is R953X, R368X, S929fsX957, R196X, V763fsX774, C715X, or R82fsX96.

38. The method of claim 35, wherein said periaxin polynucleotide is SEQ ID NO:1, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID

NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, or SEQ ID NO:77.

39. The method of claim 35, wherein said comparing step is by DHPLC, sequencing, hybridization, or a combination thereof.

40. The method of claim 35, wherein the myelinopathy is Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSN), congenital hypomyelinating neuropathy (CHN), or Roussy-Levy Syndrome (RLS).

42. The method of claim 35, wherein said mutation encodes a defect of a periaxin polypeptide, wherein the defect is E1259K, A406T, E1359delΔ, E495Q, R1132G, P1083R, I921M, A882V, T102T, P497P, or P885P.

43. A method of diagnosing myelinopathy in an individual comprising the steps of:

obtaining a sample containing nucleic acid from said individual;

assaying said sample for an alteration in a periaxin polynucleotide, wherein said alteration is associated with said myelinopathy, and wherein said myelinopathy comprises a prominent sensory neuropathy, wherein said assay provides said diagnosis.

44. The method of claim 43, wherein said periaxin polynucleotide is SEQ ID NO:76.

45. The method of claim 43, wherein said periaxin polynucleotide is SEQ ID NO:1, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID

NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, or SEQ ID NO:77.

46. The method of claim 43, wherein said assaying step further comprises a polymerase chain reaction.

47. The method of claim 46, wherein primers for said polymerase chain reaction are selected from the group consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, and SEQ ID NO:26.

48. The method of claim 43, wherein said alteration is 3775G>A, 1216G>A, 4075-4077d, 1483G>C, 3394A>G, 3248C>G, 2763A>G, 2645C>T, 306C>T, 1491C>G, 2655T>C, 2145T>A, 1102C>T, 2289delT, 2787delC, 2857C>T, or 247ΔC.

49. A method of detecting a polymorphism or mutation in a periaxin polynucleotide of an individual, comprising the steps of:

obtaining a sample comprising said periaxin polynucleotide from said individual;

assaying said periaxin polynucleotide for the polymorphism or mutation.

50. The method of claim 49, wherein said periaxin polynucleotide comprises SEQ ID NO:76.

51. The method of claim 1, wherein said myelinopathy is Dejerine-Sottas syndrome.

52. The method of claim 1, wherein said individual is suspected of having the myelinopathy.

53. The method of claim 1, wherein the alteration comprises a homozygous periaxin mutation.

54. The method of claim 1, wherein the alteration comprises a compound heterozygous periaxin mutation.

55. The method of claim 43, wherein the alteration comprises a homozygous periaxin mutation.

56. The method of claim 43, wherein the alteration comprises a compound heterozygous periaxin mutation.

57. A method of identifying an individual suspected of having myelinopathy or being a carrier of myelinopathy, comprising the steps of:

obtaining from said individual a sample comprising nucleic acid; and

assaying said sample for an alteration in a periaxin polynucleotide, wherein the presence of the alteration identifies said individual as having periaxin-associated myelinopathy or being a carrier of periaxin-associated myelinopathy.

58. The method of claim 57, wherein said myelinopathy comprises a prominent sensory neuropathy.

59. The method of claim 57, wherein the alteration comprises a homozygous periaxin mutation.

60. The method of claim 57, wherein the alteration comprises a compound heterozygous periaxin mutation.

61. A method of identifying an individual suspected of having myelinopathy or being a carrier of myelinopathy, comprising the steps of:

obtaining from said individual a sample comprising genomic DNA having two PRX alleles; and

assaying said sample for an alteration in a periaxin polynucleotide, wherein the presence of the alteration in the periaxin polynucleotide is indicative of an alteration in at least one of the PRX alleles, wherein the presence of the alteration in both PRX alleles identifies said individual as having periaxin-associated myelinopathy and wherein the presence of the alteration in one allele identifies said individual as being a carrier of periaxin-associated myelinopathy.

APPENDIX 2
EVIDENCE APPENDIX

NONE

APPENDIX 3
RELATED PROCEEDINGS APPENDIX

NONE